Conferences and Reviews

Neuroendocrine Disorders of the Gut

LAURENCE F. YEE, MD, *and* SEAN J. MULVIHILL, MD, *San Francisco, California*

The regulation of gastrointestinal function is known to involve elements of the enteric nervous system. Processes such as secretion, motility, blood flow, and immune function are all influenced by a complex network of neurons whose cell bodies lie in the gut. These neurons use a wide spectrum of substances as neurotransmitters, although the majority use peptides once thought to function only as gut hormones. It has been increasingly recognized that abnormalities of this neuroendocrine regulatory system underlie many gastrointestinal disorders. The most obvious are states of peptide excess found in patients with gut endocrine tumors such as carcinoid, gastrinoma, and somatostatinoma. Conversely, other disorders appear to be related to deficiency states. Examples include both achalasia and Hirschsprung's disease (congenital megacolon), where the loss of inhibitory neural action leads to abnormalities of peristalsis and sphincter function. Evidence for abnormal neuroendocrine regulation leading to disease states is increasing for many other gastrointestinal disorders.

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At the turn of the century, gut function was thought to be regulated only by neural influences. This view was dramatically altered by an elegant series of experiments by W. M. Bayliss and E. H. Starling demonstrating the existence of a humoral factor that stimulated pancreatic secretion.[1] In dogs, acidification of denervated proximal jejunum or the intravenous administration of crude extracts of proximal jejunal mucosa markedly increased flow of pancreatic juices. These observations led to the conclusion that the jejunal mucosa contained a factor that was released into the bloodstream to circulate and stimulate the pancreas. They named this substance secretin. This was the first demonstration of hormonal action and marked the birth of endocrinology. Over the next 70 years, further evidence of endocrine control of gastrointestinal function was found in the actions of major peptides such as gastrin and cholecystokinin.

Since the 1970s, it has been increasingly recognized that many gastrointestinal peptides are found not only in endocrine cells, but also in neurons of the brain and the gut. Increasing evidence has recently supported the concept that these neuropeptides play important roles in the regulation of diverse gastrointestinal processes, including secretion, motility, blood flow, and immune function. Thus, today, both endocrine and neural regulation of gastrointestinal function is known to be important, both in normal digestion and in disease states. In this article, we review this "neuroendocrine" regulation of gut function and its related disorders.*

*See also the editorial by R. A. Liddle, MD, "Chemical Messengers of the Gut," on pages 485-486 of this issue.

Neuroendocrine Design of the Gut

Enteric Nervous System

The enteric nervous system (ENS) is defined as the system of neurons and supporting cells found in the gastrointestinal tract, including neurons of the pancreas and gallbladder.[2] The ENS is large, encompassing 80 to 100 million nerves within the gut. Embryologically, neurons of the ENS are derived from the neural crest. These neuroblasts migrate from proximal to distal in the gut during fetal life and develop interconnected neuronal networks or plexuses of great complexity. Two major types of plexuses are present in the intestinal tract: myenteric—consisting of neurons mainly responsible for controlling peristaltic activity; and submucosal—consisting of neurons mainly responsible for controlling secretion and absorption.

Individual enteric neurons can be grouped by function or histochemical properties. The following four functional classes of enteric neurons have been identified:

- Motoneurons—efferent or effector neurons that change the activity of the intestinal smooth muscle (such as muscle contraction, blood vessel dilation);
- Secretory neurons—efferent neurons regulating endocrine or exocrine secretion;
- Sensory neurons—afferent neurons carrying information such as wall tension of the intestine or the chemical nature of its contents to the central nervous system (CNS); and
- Interneurons—neurons that add structural complexity by forming information links between other enteric neurons.

From the Division of General Surgery, Department of Surgery, Gastrointestinal Research Laboratory, University of California, San Francisco (UCSF), School of Medicine. Reprint requests to Sean J. Mulvihill, MD, Gastrointestinal Research Laboratory, UCSF, 533 Parnassus Ave, U-122, San Francisco, CA 94143-0788.

ABBREVIATIONS USED IN TEXT

APUD = amine precursor uptake and decarboxylation
CNS = central nervous system
ENS = enteric nervous system
VIP = vasoactive intestinal polypeptide

Motor and secretory neurons may be excitatory or inhibitory. Curiously, afferent neurons appear to outnumber efferent neurons in the ENS.

The substances used by enteric neurons as neurotransmitters have been identified histochemically. With this technique, five different types of neurons have been identified: cholinergic (acetylcholine), adrenergic (norepinephrine), serotoninergic (5-hydroxytryptamine), GABA-ergic (γ-aminobutyric acid), and peptidergic. Neurons containing nitric oxide synthase and using nitric oxide as a neurotransmitter have recently been identified in the gut.[3] These neurons may be separately classified as "nitrergic," but in many instances nitric oxide is co-localized with peptide neurotransmitters such as vasoactive intestinal polypeptide (VIP). Overall, peptidergic neurons are by far the largest group. Table 1 summarizes the peptides known to be present in enteric neurons.

TABLE 1.—*Neuropeptides of the Enteric Nervous System*

Vasoactive intestinal polypeptide
Peptide histidine isoleucine
Substance P
Substance K (neurokinin A)
Cholecystokinin
Somatostatin
Neuropeptide Y
Enkephalins
Dynorphin
Galanin
Calcitonin gene-related peptide
Gastrin-releasing peptide
Pituitary adenylate cyclase-activating polypeptide

Brain-Gut Axis

The ENS communicates with the CNS through both efferent and afferent pathways. This interaction has been called the brain-gut axis. Efferent CNS pathways, which may be either cholinergic or adrenergic, terminate at the level of ganglia within the gut. The release of neurotransmitters such as acetylcholine or norepinephrine activates postganglionic neurons of the ENS and influences gut function. Both efferent vagal parasympathetic and celiac sympathetic neurons function through this mechanism. Afferent pathways are composed of sensory fibers responding to stretch, noxious stimuli, and chemical changes. The stimulation of these fibers initiates the release of neurotransmitters such as substance P and calcitonin gene-related peptide, which activate local or long spinal reflexes. Extrinsic sensory neurons with cell bodies in the dorsal root ganglia allow such afferent communication from gastrointestinal tract ganglia to the CNS inferior vagal (nodose) ganglia. Many of the peptides found in enteric neurons are also present in the brain. For some peptides, such as cholecystokinin, brain concentration exceeds that of the gut. Administering these peptides to the CNS can alter gut function. In some instances, the central effect is opposite that of the peripheral effect.[4]

Gut Endocrine Cells

Endocrine cells of the gut are distinguished by their ability to produce peptide hormones from amine precursors. This *a*mine *p*recursor *u*ptake and *d*ecarboxylation led Pearse in 1966 to the APUD concept.[5] In this way, gut endocrine cells are similar to enteric neurons and cells of the hypothalamic-pituitary axis. These endocrine cells may be "open," with their apex exposed in the gut lumen, or "closed" within the organ. "Open" cells exposed to the lumen can be influenced by luminal stimuli, such as nutrients. "Closed" cells presumably detect luminal stimuli indirectly, through mechanisms that are poorly understood. The release of peptides from these cells may be into the bloodstream in classic endocrine action or into the interstitial fluid to act on nearby cells. This latter effect, called paracrine delivery, is likely an important regulatory mechanism in the gut for peptides such as somatostatin. Although endocrine cells of the gut were once thought to be derived from the

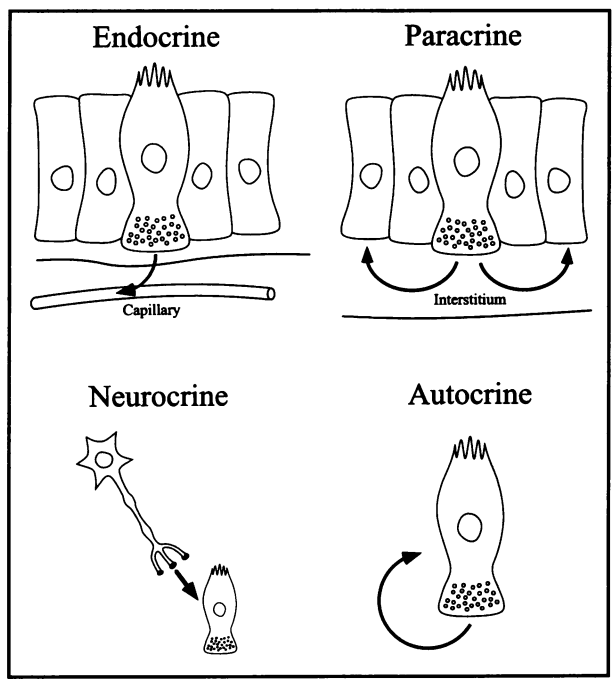

Figure 1.—The modes of the delivery of regulatory peptides to target cells are shown. In classic endocrine delivery, the hormone is secreted into the bloodstream, which carries it to the target cell. Paracrine delivery refers to the local diffusion of substances through interstitial fluid to target cells. Neurocrine delivery involves the release of substances by neurons innervating target cells. In autocrine delivery, cells release agents that affect their own function.

TABLE 2.—*Gastrointestinal Peptides and Their Major Actions*

Families of Peptides	*Major Actions*
Gastrin	
Gastrin	Stimulates gastric acid secretion
Cholecystokinin	Gallbladder contraction; pancreatic exocrine secretion
Secretin	
Secretin	Stimulates pancreatic fluid and bicarbonate secretion
Vasoactive intestinal polypeptide or peptide histidine isoleucine	Smooth muscle relaxation; intestinal secretion
Gastric inhibitory polypeptide	Enhances insulin release
Pituitary adenylate cyclase-activating polypeptide	Ileum or gallbladder contraction; pancreatic secretion
Pancreatic polypeptide	
Pancreatic polypeptide	Inhibits pancreatic exocrine secretion
Enteroglucagon	Enhances insulin release; stimulates mucosal growth
Peptide YY	Inhibits pancreatic secretion and acid secretion
Neuropeptide Y	Vasoconstriction; inhibition of pancreatic secretion
Tachykinin	
Substance P	Intestinal contraction; splanchnic vasodilation
Neurokinins A, B	Gut contraction
Opioid	
Neuromedin U	Gut contraction
Enkephalins	Gut motility inhibition
Dynorphin	Gut motility inhibition
β-Endorphin	Gut motility inhibition
Orphan	
Somatostatin	Inhibits release of other gastrointestinal peptides
Motilin	Sphincter contraction; associated with migratory motor complex
Neurotensin	Mesenteric vasodilation
Calcitonin gene-related peptide	Sensory neurotransmitter of gut reflexes
Gastrin-releasing peptide	Stimulates neural release of antral gastrin
Galanin	Inhibits insulin release; stimulates smooth muscle

neural crest, current evidence supports their endodermal origin.

Gastrointestinal Peptides

Gastrointestinal peptides are grouped into families, based on structural homology and mechanisms of release and action. Five identifiable families include those related to gastrin, secretin, pancreatic polypeptide, tachykinin, and opioids. A sixth group of gastrointestinal peptides with no known structural homology to others are called orphan peptides. These peptides, with their major actions, are listed in Table 2. Gastrointestinal peptides can be delivered to their target cells in one of four ways: endocrine, paracrine, neurocrine, or autocrine, as depicted in Figure 1. Gastrointestinal hormones, including secretin, gastrin, and cholecystokinin, are delivered to target cells in an endocrine manner through the bloodstream. Others, such as somatostatin, diffuse locally to their target in a paracrine manner. Neuropeptides, including gastrin-releasing peptide, substance P, and neuropeptide Y, are released from nerve endings and reach target cells by crossing a short synaptic gap. This is the dominant gastrointestinal peptide delivery method. Some peptides affect their own secretion, such as the inhibitory effect of somatostatin on its cell of origin, the D cell, and this is called autocrine delivery.

The release of gastrointestinal peptides is stimulated in many ways. Central effects, such as the sight, smell, and taste of food, stimulate the secretion of peptides such as gastrin by vagal efferent pathways. Peptide release is also mediated by the presence of food in the gut lumen. Examples include the stimulatory effect of amino acids on gastrin and cholecystokinin release. Other nutrients, such as fat, stimulate the release of cholecystokinin in the duodenum and peptide YY, neurotensin, and enteroglucagon from the ileum and colon. Other peptides are released in response to intraluminal pH. Examples include the release of somatostatin in response to antral acidification and secretin in response to duodenal acidification. Intestinal distention stimulates reflexes, causing the release of peptides affecting motility, such as VIP and substance P.

Gastrointestinal peptides act by binding and activating cell-surface receptors on target cells. The binding of a peptide with its receptor activates a cascade of intracellular events, resulting in the cellular response. Receptors and effectors may be part of the same molecule, or may be coupled through intermediary G proteins. Peptides such as VIP and secretin act through the second messenger, cyclic adenosine monophosphate, whereas cholecystokinin, gastrin, and acetylcholine act through diacylglycerol and intracellular calcium.

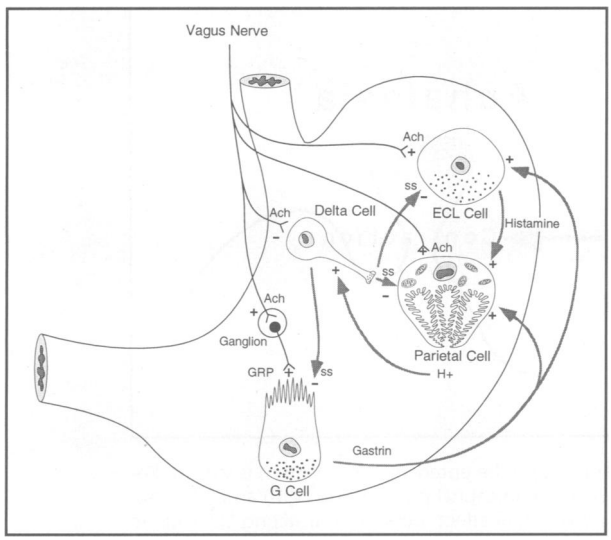

Figure 2.—The neuroendocrine control of gastric acid secretion is shown. Ach = acetylcholine, ECL = enterochromaffin-like, ss = somatostatin, GRP = gastrin-releasing peptide, + = stimulation, – = inhibition

Activation of these second messengers stimulates protein kinases and initiates cellular responses such as contraction, relaxation, and secretion.

Functions of the Enteric Nervous System

Regulation of Secretion

The ENS plays an important role in the regulation of both exocrine and endocrine secretion of the gut. These processes are best exemplified by the control of parietal cell function, a complex interplay of endocrine, neurocrine, and paracrine functions. At the thought, sight, smell, or taste of food, brain-stem vagal nuclei activate vagal efferent cholinergic fibers to stimulate postganglionic cholinergic neurons of the ENS within the gastric wall. The release of acetylcholine by these neurons stimulates parietal cell hydrogen ion secretion directly. Other cholinergic vagal efferent neurons stimulate enterochromaffin-like cells to release histamine that, in turn, stimulates parietal cell acid secretion through a paracrine pathway. Additional vagal efferent neurons stimulate the release of gastrin-releasing peptide from ENS neurons. Gastrin-releasing peptide stimulates antral G cells to release gastrin into the blood. Circulating gastrin potently stimulates the parietal cell directly by binding to parietal cell gastrin receptors and indirectly by stimulating enterochromaffin-like cell histamine release. Finally, central cholinergic stimulation also increases acid secretion through the inhibition of the release of somatostatin from gastric D cells. On emptying of a meal from the stomach, somatostatin provides feedback inhibition of further parietal cell acid secretion. Somatostatin is released in response to antral acidification and inhibits acid secretion indirectly by inhibiting G-cell gastrin release[6] and enterochromaffin-like cell histamine release and directly by inhibiting parietal cells.[7] These pathways are summarized in Figure 2. Other secretory processes regulated by the ENS include pancreatic exocrine secretion by gastropancreatic and enteropancreatic reflexes and intestinal and colonic secretion by neurons containing VIP.

Regulation of Motility

Gastrointestinal smooth muscle cells are controlled predominantly by the ENS, but are subject to additional endocrine and CNS influence. The three most important aspects of gastrointestinal motility are peristalsis, the migratory motor complex, and sphincter function.

Peristalsis is coordinated contraction and relaxation of the gut that results in the distal transit of a meal. This process is intrinsic to the gut and occurs even after extrinsic denervation. It is now known that peristalsis is regulated by the ENS. The mechanisms of ENS regulation of peristalsis have been determined largely from studies of isolated intestinal muscle strips. Stretch stimulation initiates a proximal contraction reflex that appears to be mediated by neurons using acetylcholine and substance P as neurotransmitters. Simultaneously, intestinal stretch induces a distal relaxation reflex, allowing the propagation of the meal. This reflex is mediated by neurons containing VIP and nitric oxide as neurotransmitters.[8,9]

The migratory motor complex refers to the strong propulsive wave observed at regular intervals in the fasted state that sweeps down the entire gut, clearing it of food particles. The migratory motor complex has been appropriately called the "housekeeper" of the gut and probably serves to prevent intestinal bacterial overgrowth, stasis, and malabsorption. The migratory motor complex originates from a gastric pacemaker on the proximal greater curvature and migrates distally down the gut in four recognizable phases. Although vagotomy and sympathectomy do not alter the complex, the ingestion of food abolishes it and returns the intestine to a fed pattern. The major propulsive wave occurs during phase III of the motor complex. This phase has been associated with a rise in serum motilin levels, but a cause-and-effect relationship has not been established.

The relaxation and contraction of the sphincters of the gut, including those of the lower esophagus, pylorus, ampulla of Vater, ileocecal valve, and internal anal sphincter, are regulated by the ENS. In general, nitric oxide and "VIPergic" neurons mediate relaxation, and either or both cholinergic and adrenergic neurons mediate the contraction of sphincters.

Neuroendocrine Disorders of the Gut

Better understanding of normal gut function has led to the clarification of the pathophysiology of some heretofore mysterious gastrointestinal disorders. The complex nature of the regulatory processes in the gut and the diffuse nature of the gut neuroendocrine system have made the study of these disorders difficult. In addi-

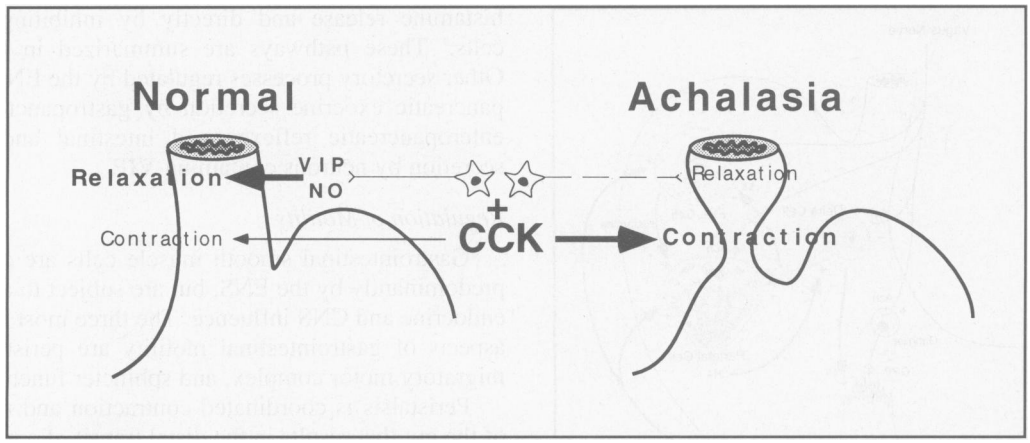

Figure 3.—The regulation of the lower esophageal sphincter (LES) by the enteric nervous system is shown. Relaxation of the LES is caused by inhibitory neurons using vasoactive intestinal polypeptide (**VIP**) and nitric oxide (**NO**) as neurotransmitters. Cholecystokinin (**CCK**) likely has a dual effect: directly contracting LES muscle fibers and indirectly relaxing the LES by stimulating VIP- and NO-containing neurons. In normal persons, the inhibitory mechanisms predominate. In patients with achalasia, the inhibitory neural reflexes are lost, resulting in a tonically contracted, high-pressure LES.

tion, unlike other endocrine organs such as the thyroid or adrenal gland, states of regulatory peptide excess or deficiency have not always been easily recognizable as diseases. Several disorders of gut function have now been attributed to abnormalities of neuroendocrine regulation. These disorders are summarized as follows.

Achalasia

Achalasia is an esophageal motility disorder characterized by abnormal or absent peristalsis in the body of the esophagus, a high-pressure lower esophageal sphincter, and failure of the lower esophageal sphincter to relax with deglutition. These functional abnormalities are due to defects in ENS regulation of esophageal motility, which is mainly due to a loss of inhibitory neurons. An impairment of inhibitory neuron function is demonstrated by the paradoxical increase in lower esophageal sphincter pressure observed in response to cholecystokinin in patients with achalasia.[10] Immunochemical studies reveal a decreased number of or absent VIPergic and nitrergic neurons in the lower esophagus and the lower esophageal sphincter in patients with achalasia.[11,12] The intravenous administration of VIP decreases lower esophageal sphincter pressure in patients with achalasia, but not normal persons, suggesting that in achalasia, the lower esophageal sphincter may be supersensitive to VIP.[13] Although lower esophageal sphincter pressure can sometimes be reduced with long-acting nitrates or calcium channel blockers, many patients require myotomy of the sphincter. Its regulation is summarized in Figure 3.

Chagas' Disease

Chagas' disease is caused by infestation with the parasite *Trypanosoma cruzi*. This parasite produces a neurotoxin that causes irreversible damage to submucosal and myenteric neural plexuses throughout the body. Gastrointestinal manifestations of this neuropathy include megaesophagus due to failure of the lower esophageal sphincter to relax and dilation of both the small bowel and colon due to the failure of peristalsis.

Gastric Dysrhythmias

Unexplained vomiting is occasionally found to be due to abnormal gastric electrical activity, referred to as gastric dysrhythmia. Several patterns of abnormal electrical activity have been identified. In some patients, an ectopic gastric pacemaker is present, leading to tachygastria.[14] This ectopic pacemaker disrupts phase III of the migratory motor complex, with uncoupling of fundic and antral coordination, resulting in poor antral grinding and delayed gastric emptying. An abnormal gastric electrical pattern has also been observed in patients with postoperative ileus, motion sickness, diabetic gastroparesis, and anorexia nervosa. Some of these patients benefit from promotility agents, including metoclopramide hydrochloride (a dopamine antagonist that acts as a cholinomimetic in the antrum), cisapride (which enhances acetylcholine release at peripheral gut sites), and erythromycin (an antibiotic that activates gut motilin receptors).

Hypertrophic Pyloric Stenosis

Pyloric stenosis is a congenital obstructing lesion found most commonly during the first six months of life. Histologic findings include pyloric muscle hypertrophy, mucosal edema, and submucosal lymphocytic infiltration, without notable anatomic changes in ganglia. Although its pathogenesis is unknown, defects in ENS regulation of the sphincter appear to play a role. For example, nitric oxide synthase is lacking in pyloric tissue from infants with pyloric stenosis.[15] In addition, in genetically altered mice lacking the neuronal nitric oxide synthase gene, a disorder resembling human pyloric stenosis develops, with grossly enlarged stomachs and hypertrophy of the pyloric musculature.[16]

Previous studies have suggested that abnormalities of other gut peptides may play a pathogenic role, as the administration of exogenous pentagastrin to pregnant dogs induces pyloric hypertrophy in some offspring.[17] Surgical pyloromyotomy remains the preferred treatment method.

Scleroderma

Scleroderma, a multisystem disorder characterized by obliterative vasculitis and the proliferation of connective tissue, can affect the gastrointestinal tract from the mouth to the anus. Gastrointestinal symptoms include pain, bloating, dysphagia, constipation, and malabsorption. Defects in esophageal motility, gastric emptying, and intestinal peristalsis have been identified. Electrical activity corresponding to phase III of the migratory motor complex is diminished in amplitude and frequency in patients with scleroderma, whereas serum motilin levels are elevated.[18] Administering the somatostatin analogue octreotide increases the frequency of the migratory motor complex and reduces malabsorption and symptoms in severely afflicted patients.[19] Although the mechanism of this effect is unclear, somatostatin is a neurotransmitter in myenteric neurons of the small and large intestine and stimulates myenteric acetylcholine release.[20]

Irritable Bowel Syndrome

The irritable bowel syndrome is a functional motor disorder characterized by alternating constipation and diarrhea and abdominal pain in the absence of detectable organic disease. Recent evidence suggests that this group of disorders may be caused by alterations in the regulation of gut motility by the ENS. Administering cholecystokinin increases colonic activity and abdominal pain in some patients with the irritable bowel syndrome, suggesting that meal-induced cholecystokinin release may account for postprandial pain.[21] In addition, an alteration in the sensitivity of gut afferent neurons, mediating the perception of pain, is thought to contribute to this syndrome. Patients with the irritable bowel syndrome have an increased perception of pain in response to sigmoid balloon dilation compared with control patients.[22] Heightened sensitivity of visceral afferent neurons to normal endogenous stimuli may play a role in other functional bowel diseases such as noncardiac chest pain and nonulcer dyspepsia.

Inflammatory Bowel Disease

The ENS plays a major role in modulating the gut immune response. Recent evidence suggests that alterations in the ENS are involved in the pathophysiology of inflammatory bowel disease. Neuropeptides such as substance P, VIP, enkephalin, and somatostatin alter lymphocyte function.[23] Conversely, cytokine products of the immune system have clear effects on gut function. In patients with Crohn's disease, the number of rectal VIPergic neurons is increased immunohistochemically, as are concentrations of rectal mucosa VIP.[24] Furthermore, the number of substance P receptors is increased in colon from patients with inflammatory bowel disease.[25] The expression of several recently described neuropeptides, the trefoil peptides, may also be found in patients with inflammatory bowel disease.[26] In addition to this evidence of abnormalities in gut peptides, other studies have identified increased circulating and mucosal cytokine production in patients with inflammatory bowel disease.[27,28] Thus, this disease may be related to alterations in immune-ENS interactions that result in inflammation and diarrhea. This area is currently the subject of intensive investigation.

Pseudo-obstruction

A few patients present with features of intestinal obstruction in the absence of any mechanical lesion. This so-called intestinal pseudo-obstruction has both acute and chronic forms. Both appear to be caused by abnormalities in the regulation of peristalsis by the ENS. Chronic intestinal pseudo-obstruction may be acquired, but it also has a familial form. Abnormalities of intestinal ganglia have been identified immunocytochemically in patients with chronic intestinal pseudo-obstruction.[29] No uniform pattern has been found, however, suggesting that this disorder may represent the clinical expression of any one of several regulatory defects. The administration of cisapride relieves symptoms in some patients with chronic pseudo-obstruction, but no therapy has proved uniformly beneficial.[30]

Chronic Constipation

Although the cause of chronic constipation is varied, some patients appear to have abnormalities in ENS regulation of colonic motility. Three patterns of abnormal motility have been identified: generalized aperistalsis, rectosigmoid junction dysmotility, and anal sphincter dysfunction.[31] Studies of patients with chronic constipation suggest that colonic VIP levels are decreased or absent and that serotonin levels are increased.[32,33]

Hirschsprung's Disease

Hirschsprung's disease is one of the most clearly documented disorders of gut function related to defects in the ENS. Afflicted patients present with colon obstruction in infancy or, more rarely, with chronic constipation in adulthood. This disorder is due to the absence of intramural ganglion cells in the colon and rectum. The aganglionic segment always involves the internal anal sphincter and has variable extension proximally. The congenital defect is thought to be due to an arrest in caudad migration of neuroblasts from the neural crest to the distal gut during development.[34] Histologically, abundant hyperplastic neurons are present in the gut wall, but ganglion cells are absent. The absence of relaxant enteric neurons and ganglia containing VIP and nitric oxide in the involved segments is thought to cause the pronounced colonic spasticity seen in patients with Hirschsprung's disease.[35-37] Other peptides, including substance P, may also have a role.[38]

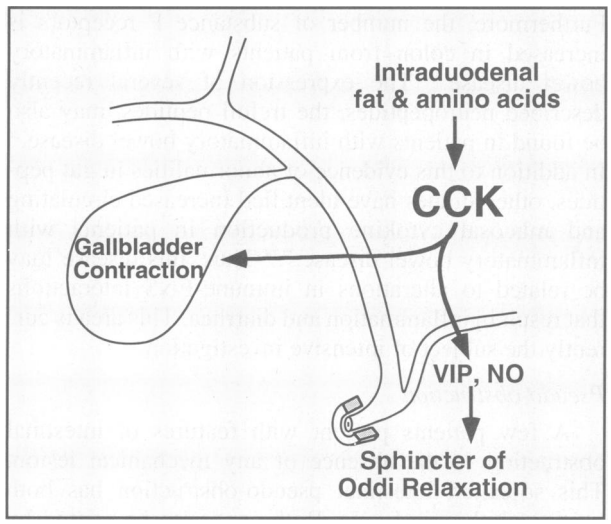

Figure 4.—The regulation of sphincter of Oddi function by the enteric nervous system is shown. With the ingestion of a meal, intraduodenal fat and amino acids cause the release of cholecystokinin (**CCK**) from duodenal endocrine cells. Cholecystokinin has a dual action, directly causing gallbladder contraction and simultaneously causing relaxation of Oddi's sphincter. This latter effect is indirect and mediated by the release of vasoactive intestinal polypeptide (**VIP**) and nitric oxide (**NO**) from inhibitory neurons innervating sphincter smooth muscle.

At present, resection of the involved colonic segment is the treatment of choice for patients with Hirschsprung's disease.

Sphincter of Oddi Dyskinesia

About 10% of patients undergoing evaluation of postcholecystectomy pain are found to have abnormal tonic or stimulated sphincter of Oddi motility. The regulation of function of Oddi's sphincter is under the control of neurons of the ENS. In humans, cholecystokinin contracts the gallbladder and decreases both basal tone and phasic wave activity in the sphincter. As shown in Figure 4, this last effect is indirect and mediated by VIP and nitric oxide release from inhibitory sphincter neurons. In some patients, the administration of exogenous cholecystokinin causes a paradoxical increase in sphincter tone concomitant with gallbladder contraction, resulting in pain.[39] This suggests a loss of inhibitory innervation akin to that observed in achalasia. Direct neural connections from the gallbladder to the sphincter mediating relaxation have been identified. It is possible that cholecystectomy, in some patients, may alter these reflex pathways.

Endocrine Tumors of the Gut

The rare examples of peptide excess states leading to disorders of gastrointestinal function are related to tumors that secrete gut peptides and amines. These tumors, although uncommon, have provided important insights into the physiologic effects of their secretory products. A summary of the major endocrine tumors of the gut is given in Table 3. Although a given tumor secretes a dominant peptide, leading to a clinically identifiable syndrome, many gut endocrine tumors release multiple peptide products. These lesser products (such as somatostatin) occasionally ameliorate the clinical symptoms. Radiolabeled peptides, octreotide and VIP, have recently been used successfully to localize these interesting tumors.[40,41]

Carcinoid Syndrome

Carcinoids are APUD tumors, and although they occur throughout the length of the gastrointestinal tract, 95% originate in one of three sites: the appendix, rectum, or ileum. Although the endocrine products of the primary tumor are metabolized by the liver, in the face of metastatic disease or bronchial or ovarian primary, they may circulate and cause the carcinoid syndrome, manifested mainly by flushing and diarrhea. Associated conditions include asthma, valvular heart disease, and pellagra. Carcinoid tumors release a number of peptide

TABLE 3.—*Major Endocrine Tumors of the Gut*

Tumor	*Cell Type*	*Clinical Features*
Carcinoid	Enterochromaffin or enterochromaffin-like	Cutaneous flushing, diarrhea
Gastrinoma	G cell, islet non-β cell	Peptic ulceration, diarrhea
Vipoma	Islet D_1 cell	Verner-Morrison or WDHA syndrome: watery diarrhea, hypokalemia, achlorhydria
Somatostatinoma	Islet D cell	Diabetes mellitus, steatorrhea, gallstones
Insulinoma	Islet β cell	Whipple's triad: low fasting blood glucose level (<2.5 mmol/liter), symptoms of hypoglycemia induced by fasting (such as trembling, weakness, mental confusion), and relief of symptoms by oral or intravenous glucose
Glucagonoma	Islet A cell	Mild diabetes, migratory necrolytic erythema, glossitis
PPoma	Islet PP cell	Usually clinically silent

products, including serotonin (5-hydroxytryptamine), substance P, histamine, kallikrein, and neurotensin. The metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), is found in the urine and is widely used as a tumor marker. The symptoms of the carcinoid syndrome are caused by the secretion of these vasoactive amines and peptides. The watery diarrhea, caused by rapid transit in the intestinal tract,[42] may be due to circulating serotonin, as this symptom can be abolished with the administration of serotonin antagonists. Bradykinin, neurotensin, and substance P appear responsible for flushing. Tumor substance release can be inhibited and symptoms palliated with the administration of octreotide. Selected patients benefit from cytotoxic chemotherapy or surgical resection.

Gastrinoma

In 1955, Zollinger and Ellison described a syndrome of severe peptic ulcer disease and gastric acid hypersecretion associated with non-β-islet cell tumors of the pancreas.[43] After the development of radioimmunoassay, it was proved that gastrin was the cause of this syndrome. Although they were initially described as pancreatic tumors, it has been increasingly evident that a substantial fraction of these tumors arise in extrapancreatic sites, particularly the duodenum. Peptic ulceration, which occurs in more than 90% of patients, is due to parietal cell stimulation by the potent secretagogue gastrin. Gastrin also causes a pronounced gastric epithelial hypertrophy. The diarrhea in gastrinoma is caused by the delivery of large volumes of acidic gastric contents to the small bowel and the stimulation of intestinal peristalsis by circulating gastrin. Increased luminal acid inactivates pancreatic lipase, resulting in steatorrhea. Although administering the hydrogen-potassium-adenosine triphosphatase inhibitor omeprazole effectively treats symptoms of gastrinoma by blocking parietal cell acid secretion, 50% of patients die of metastatic gastrinoma. Thus, surgical resection, when possible, is the optimal treatment of patients with these tumors.

Vipoma

Vipomas are rare neuroendocrine tumors that secrete excessive amounts of VIP. More than 80% are localized to the pancreas, and about 60% are malignant. The excess production of VIP by these tumors accounts for the clinical syndrome of *w*atery *d*iarrhea, *h*ypokalemia, and *a*chlorhydria (WDHA syndrome).[44] The excess VIP causes small intestinal and colonic secretion of bicarbonate- and potassium-rich fluid, leading to alkaline diarrhea, hypovolemia, hypokalemia, and metabolic acidosis. Vasoactive intestinal polypeptide also inhibits acid secretion, resulting in hypochlorhydria or achlorhydria. Diagnosis is made by identifying elevated plasma VIP levels associated with large-volume secretory diarrhea. The medical treatment of choice is the use of the somatostatin analogue octreotide, which controls diarrhea in more than 80% of patients.[45] Surgical excision should be considered in all patients without metastatic disease.

Somatostatinoma

Somatostatinomas are rare endocrine tumors usually found in the pancreas or duodenum. About 80% have metastasized by the time of diagnosis. These tumors produce and release large amounts of somatostatin. The elevated circulating somatostatin levels cause a distinct clinical syndrome of mild diabetes mellitus, gallstones, steatorrhea, and weight loss. The diabetes is caused by the inhibition of islet insulin release by somatostatin. The diabetes is usually mild, probably due to a concomitant inhibition of glucagon release. Gallstones likely result from the inhibition of gallbladder emptying by somatostatin. This effect may occur both by a direct inhibition of gallbladder motility and indirectly through the inhibition of cholecystokinin release. Steatorrhea is caused by the profound inhibition of pancreatic enzyme secretion by somatostatin. At present, surgical resection and chemotherapy are the main therapeutic options.

Other Gut Endocrine Tumors

The most common pancreatic islet cell tumor is insulinoma, but this tumor rarely causes gastrointestinal symptoms. Similarly, glucagonoma is virtually never found in extrapancreatic primary sites and rarely presents with gastrointestinal symptoms. Much more rarely encountered are tumors secreting pancreatic polypeptide ("PPoma"). These tumors usually arise in the head of the pancreas and are ordinarily clinically silent. Tumors have occasionally been reported to cause diarrhea or peptic ulceration, but it is possible that these effects are caused by peptide products of the tumors rather than pancreatic polypeptide itself.

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